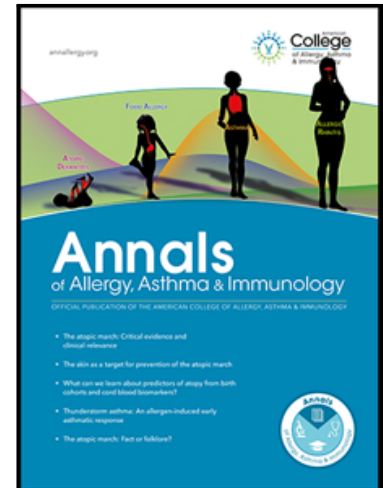


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Impact of Nasal Polyps on Endotype and Phenotype in Moderate to Severe Asthma Patients

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Title: Impact of Nasal Polyps on Endotype and Phenotype in Moderate to Severe Asthma Patients

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Abbreviations

ACQ	asthma control questionnaire
AERD	aspirin exacerbated respiratory disease
A	asthma only
AR	allergic rhinitis
ATS	American thoracic society
AX	area under reactance curve
AwNP	asthma with nasal polyps
BMI	body mass index
CRSwNP	chronic rhinosinusitis with nasal polyps
CT	computed tomography
ERS	European respiratory society
FEF ₂₅₋₇₅	forced expiratory flow between 25 and 75% of forced vital capacity
FeNO	fractional exhaled nitric oxide
FEV ₁	forced expiratory volume in 1 second
FVC	forced vital capacity
F _{res}	resonance frequency
ICS	inhaled corticosteroid
IgE	immunoglobulin type E
IL	interleukin
ILC2	type 2 innate lymphoid cells
IOS	impulse oscillometry
INAH	intranasal antihistamine

58	INS	intranasal corticosteroid
59	LABA	long acting beta agonist
60	LAMA	long acting muscarinic antagonist
61	LM	lund mackay
62	LTRA	leukotriene receptor antagonist
63	NHS	National Health Service
64	NPS	nasal polyp score
65	OCS	oral corticosteroid
66	PBE	peripheral blood eosinophils
67	R5	resistance at 5 Hz
68	R5-R20	difference between resistance at 5 and 20 Hz
69	R20	resistance at 20 Hz
70	SAD	small airways dysfunction
71	SEM	standard error of means
72	T2	type 2 inflammation
73	THEO	theophylline
74	X5	reactance at 5 Hz

75

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79

80 **Key words:** allergy, ACQ, chronic rhinosinusitis, nasal polyps, exacerbations, fractional
81 exhaled nitric oxide, peripheral blood eosinophils, severe asthma, small airways dysfunction,
82 type 2 inflammation

83

84 **INTRODUCTION**

Severe refractory type 2 (T2) asthma presents a significant challenge to physicians due to disease heterogeneity, heavy symptom burden, high healthcare consumption costs and concomitant T2 comorbidities.(1) Chronic rhinosinusitis with nasal polyps (CRSwNP) is a common comorbidity directly related to asthma severity,(2) with an approximate prevalence of 30% amongst severe refractory asthmatics.(3) Both conditions are thought to follow the common pathophysiological mechanism of T2 inflammation, typically characterised by increased cytokine expression of IL4, IL5 and IL13 in response to various triggers.(4)

Recently, clinicians have used T2 biomarkers such as peripheral blood eosinophils (PBE), fractional exhaled nitric oxide (FeNO) and allergic status (specific and total IgE) to classify severe asthma patients according to their underlying inflammatory endotype.(1) Eosinophilic proliferation, maturation, survival, activation and migration is governed by IL5, whilst IL13 is associated with FeNO as well as eosinophil tissue migration.(1)

The mainstay therapy for both CRSwNP and asthma consists of inflammatory suppression with local corticosteroids, followed by short courses of systemic corticosteroids for exacerbations.(2) CRSwNP patients refractory to medical therapy have traditionally been referred for consideration of functional endoscopic sinus surgery.(5) Promising results have been reported with anti-IgE, anti-IL5 and anti-IL4 α , proposed to target 'treatable traits' according to presence of T2 biomarkers in CRSwNP and asthma.(2) Although all three classes of biologics have resulted in significant improvements in key CRSwNP outcomes (NCT03085797) at the standard licensed subcutaneous doses used in concomitant asthma,(6, 7) an indirect treatment comparison of omalizumab versus dupilumab in CRSwNP has demonstrated significantly greater improvements with the latter.(8) Notably, omalizumab and dupilumab are entering into mainstay therapy for the treatment of nasal polyps in the US, having been approved by the Food and Drug Administration. Nonetheless, further research is

required to determine the impact of endotype on patient response to biologics with regard to NP.

In a recent study of severe asthma patients, PBE >420 cells/ μ l and FeNO ≥ 39 ppb were found to be the best predictors of concomitant NP.(9) Furthermore, patients with allergic asthma and concomitant allergic rhinitis (AR) exhibit higher levels of PBE and FeNO whilst having lower FEV₁% and FEF₂₅₋₇₅% compared to those with allergic asthma alone.(10) Although one study demonstrated that non-asthmatic patients with CRSwNP may have evidence of small airways dysfunction (SAD) measured by spirometry,(11) to our knowledge no studies have been performed to evaluate SAD with spirometry or impulse oscillometry (IOS) in asthma patients with CRSwNP. In contrast to spirometry, IOS involves a tidal breathing manoeuvre used to measure small airways function by assessing peripheral airway resistance as difference in resistance between 5 and 20 Hz (R5-R20), peripheral airway reactance as area under reactance curve (AX) and reactance at 5 Hz (X5), and resonance frequency (fres).

Therefore, we performed a retrospective analysis to identify putative differences in T2 biomarkers, lung function and asthma control in asthma patients with nasal polyps (AwNP) compared to those with asthma alone (A).

METHODS

Database

140 consecutive moderate to severe asthma patients with or without endoscopic NP taking a daily beclomethasone dipropionate (BDP) equivalent inhaled corticosteroid (ICS) dose $\geq 800\mu$ g and at least one second line controller (LABA, LAMA, LTRA or theophylline) were identified from our National Health Service (NHS) specialist respiratory and rhinology clinics over a period of 3 years. CRS patients without endoscopic NP were excluded. Data on

132 PBE, FeNO, allergic status, spirometry, IOS, asthma control questionnaire (ACQ), oral
133 corticosteroid (OCS) requiring asthma exacerbations, nasal polyp score (NPS) and LM score
134 were retrospectively collected. Values for all T2 biomarkers and lung function were taken
135 prior to initiation of any biologics as these can affect PBE, FeNO and IgE. Values for PBE
136 were taken as the mean of values over the previous year.

137 FeNO was measured using NIOX VERO (Circassia, Oxford, UK) according to
138 manufacturer's instructions and ATS/ERS guidelines.(12) Blood testing was performed to
139 detect presence of circulating levels of specific IgE antibodies to defined common allergens
140 [Fluorescence enzyme linked immunoassay (Phadia Immunocap 250)]. In our NHS
141 laboratory a specific IgE concentration greater than 0.35 kUA/L is considered a positive
142 result. We characterised specific allergy for each patient either as: (a) number of positive
143 specific IgE responses to aeroallergens including cat, dog, silver birch, house dust mite and
144 grass, and (b) mean specific IgE calculated as the sum of specific IgE in kUA/L divided by
145 the number of aeroallergens tested.

146 Spirometry (Micromedical, Chatham, UK) was performed according to American Thoracic
147 Society (ATS) and European Respiratory Society (ERS) guidelines.(13) Prior to attending the
148 laboratory for spirometry, patients had been asked not to use their short acting beta-2 agonists
149 for 6 hours, long acting beta-2 agonists and muscarinic antagonists, theophyllines and
150 leukotriene receptor antagonists for 48 hours. IOS (Masterscreen, Carefusion Hoechberg,
151 Germany) measurements were performed in triplicate according to the European Respiratory
152 Society guidelines(14) with IOS always performed prior to spirometry. Accuracy of
153 resistance measurements was confirmed on each day with a 3L calibration syringe and a
154 standard 0.2 kPa/L/s resistance mesh. Nasal endoscopy (30° oblique rigid Hopkins 3.0 mm)
155 was performed in our rhinology mega-clinic to obtain NPS with a maximum score of 8. Lund
156 Mackay scores were calculated from the most recent CT scan to radiologically assess

CRSwNP burden with a maximum score of 24. Patients with aspirin exacerbated respiratory disease (AERD) were identified through history.

Statistical Analysis

Data were first analysed for normality using Boxplots. FeNO and specific IgE (kUA/L) values were logarithmically transformed prior to analysis to normalise their distribution. Receiver operating characteristic curves were plotted to determine pre-test probability of NP based on FeNO values. Independent Student's T-tests with alpha error set at 0.05 (2-tailed) were applied. Values are presented as arithmetic means (SEM) and geometric means (SEM) for FeNO and specific IgE.

Ethics

Caldicott Guardian approval was obtained to allow access to any NHS patient identifiable data including allergy, PBE, FeNO, spirometry, IOS, ACQ, asthma exacerbations, NPS and LM score.

RESULTS

Table 1 depicts demographic data showing patients in the AwNP group were more likely to be male and older than those in the A group. 29/78 (37%) and 5/62 (8%) were taking maintenance OCS in the A and AwNP groups respectively. A subgroup of 63/140 (45%) also had measurement of IOS. 27 (A, n=22; AwNP, n=5) and 55 (A, n=37; AwNP, n=18) patients subsequently commenced biologic treatment for asthma with either anti-IgE or anti-IL5 therapy respectively.

In the overall analysis (Table 1), PBE and FeNO were significantly higher whilst total and specific IgE were significantly lower in the AwNP group (Figure 1). Receiver operating characteristic (ROC) curves demonstrated that FeNO ≥ 22 ppb had sensitivity and specificity

values of 81% and 67% respectively for the association of NP (AUC=0.76, $p=0.001$) whilst PBE ≥ 324 cells/ μ l had sensitivity and specificity values of 80% and 46% respectively (AUC 0.67, $p=0.003$).

AwNP patients had better asthma control as reflected by fewer exacerbations, a lower ICS dose and less impairment of IOS values (R5, R5-R20, X5 and AX). No significant differences in spirometry values were demonstrated between the two groups. The findings were similar when excluding the presence of allergic rhinitis (20/78) among asthma patients without NP (Table 2) and also among patients (AwNP, $n=37$; A, $n=70$) taking at least 1,500 μ g ICS. However, in the sub-analysis of patients taking at least 1,500 μ g ICS, no significant differences in total or specific IgE were detected.

No significant differences in T2 biomarkers, lung function or asthma control were demonstrated when comparing AwNP patients with aspirin exacerbated respiratory disease (AERD) ($n=25$) to AwNP patients without aspirin sensitivity ($n=37$). However, LM scores were significantly higher in AERD patients: 19(1) vs 15(1); $p<0.01$.

In the AwNP group, patients with a NPS $\geq 5/8$ had significantly higher LM scores than those with NPS $< 5/8$: 18(1) vs 14(1); $p<0.05$. The overall mean LM score in the AwNP group was 16(1).

When excluding patients on maintenance OCS, PBE and FeNO values remained significantly higher in the AwNP group: 549(41) vs 393(31) $p<0.01$ for PBE and 44(9) vs 20(9) $p<0.05$ for FeNO.

DISCUSSION

Our patients without NP had worse asthma control in terms of more frequent exacerbations and associated higher ICS dose, which was mirrored by worse IOS but not spirometry. This is

likely to reflect worse small airways dysfunction (SAD) defined by raised peripheral airway resistance (R5-R20) and peripheral airway reactance (AX or X5). Our data also showed that asthma control in more severe asthma patients is more closely related to SAD detected by IOS rather than spirometry, since FEF_{25-75} was not significantly different.(15) Although speculative, the significant differences in IOS measurements between the two groups could hypothetically be explained by the presence of two separate conditions on the same disease spectrum. It could be argued that one condition is characterised by inflammation of the nose, paranasal sinuses and larger airways whilst the other involves more distal portions of the bronchial tree. Further research is required to prove this theory and would provide more support for the incorporation of IOS into the standard work up for severe asthma.

In a recent large prospective study, the ATLANTIS group demonstrated that R5-R20 and AX measurements showed comparable prevalence of SAD in asthma patients at severities of GINA 1-3, a higher prevalence at GINA 4 and the highest prevalence at GINA 5.(16) Furthermore, one study aiming to validate the use of forced oscillation R5-R20 using computational models as a measure of small airway narrowing identified 0.08kPa/L/s as representing severe SAD.(17) However, more work is still required for the standardisation of IOS measurements and the establishment of normal ranges. A previous comparison between two forced oscillation devices, IOS Jaeger Masterscreen and airway oscillometry (AOS) Thorasys Tremoflo, has shown better agreement for small airways resistance rather than reactance, and that AOS may be more sensitive at measuring reactance in patients with airflow obstruction.(18)

The results of the present study also showed that the presence of NP in asthma patients was associated with higher PBE and FeNO, lower total and specific allergy burden, whilst asthma control was better along with less small airways dysfunction. The higher PBE and FeNO in AwNP patients is perhaps expected as one might predict that two concomitant T2 conditions would be associated with a higher T2 burden than one alone.(1) According to ROC analysis,

228 FeNO showed superior ability than PBE in determining the presence of NP in our cohort of
229 asthma patients. FeNO levels were normal in our asthma patients without NP but previous
230 literature shows that even a modest ICS dose, fluticasone propionate 100µg/day, can
231 produce a 52% FeNO suppression from baseline in mild to moderate asthma.(19) We took
232 care to document PBE and FeNO values prior to patients commencing biologic therapy to
233 avoid confounding. Average PBE counts over the preceding year were calculated as temporal
234 variability in blood eosinophils is an important consideration.(20) In contrast, total and
235 specific IgE were significantly lower in our patients with NP in line with a previous
236 study.(21) Since dupilumab inhibits signalling of IL4 and IL13 suppressing both IgE and
237 FeNO, this perhaps might in part explain why it is highly effective in treating both asthma
238 and NP.(7)

239 As PBE count has previously been reported to be associated with worse IOS outcomes(22)
240 we were somewhat surprised to find that IOS measurements were worse in our asthma
241 patients without NP where PBE count was lower. Although ACQ was numerically lower in
242 patients with NP, the difference of 0.6 between groups was not significant, which is
243 somewhat surprising given that ACQ is a strong predictor of exacerbations.(23, 24) As
244 expected, our AwNP patients with AERD exhibited higher LM scores than those without
245 aspirin sensitivity, reflecting a greater degree of underlying sinus inflammation in line with
246 previous literature.(25)

247 Notably similar trends between groups were still observed when excluding group A patients
248 without allergic rhinitis. We felt this was important to ascertain given patients with asthma
249 and allergic rhinitis have worse lung function and higher T2 biomarkers than patients with
250 asthma alone.(10)

We accept our study has several limitations. Firstly, our study was retrospective and did not look at serial changes over time, including the potential impact of instigating biologic therapy. In a five-year prospective follow-up study of 200 newly diagnosed asthma patients, accelerated decline in FEV₁ was associated with nasal polyps, PBE and FeNO.(26) Moreover, we have recently shown that biologic therapy improves IOS measurements in severe asthma patients with baseline SAD, where NP prevalence was comparable to previous literature estimates.(27) We do not believe that the limited sample size was relevant here as otherwise we would have missed important differences in outcomes such as asthma exacerbations, ICS dose and IOS. Perhaps a larger sample size might have picked up commensurate differences in ACQ and spirometry, although we feel this is somewhat unlikely given the greater improvements in exacerbations compared to either ACQ or FEV₁ in T2 high asthma patients treated with biologics.(28, 29) There may have been a confounding effect from differences observed in ICS dose since this is known to suppress FeNO and PBE levels.(30) However, in the sub-analysis of patients on ICS $\geq 1,500\mu\text{g}$ where no significant ICS dose difference was found, FeNO and PBE were still significantly higher in the AwNP group. Moreover, exclusion of patients on maintenance OCS also resulted in significantly higher PBE and FeNO levels in the AwNP group. Repeat analysis was also performed with the exclusion of current smokers, due to their association with suppressed FeNO, yielding similar results to the original analysis.

The results of our study suggest that it may be worthwhile to consider investigating moderate to severe asthma patients with raised PBE and FeNO levels for sino-nasal disease with nasal endoscopy and CT imaging especially those with impaired sense of smell, as this may have subsequent treatment implications. In conclusion, moderate to severe asthma patients with NP have higher levels of PBE and FeNO but lower total and specific allergy than those without NP. Patients without NP had greater small airways dysfunction in association with

276 worse control. Taken together this reinforces the importance of careful characterisation of
277 endotype and phenotype in patients with moderate to severe asthma.

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356 **Table 1**

357 **Baseline Demographic Data and Comparisons in Type 2 Biomarkers, Lung Function and Asthma**
 358 **Control**

	AwNP (SEM)	A (SEM)
Gender (F/M)	28/34	56/22
Age (yrs)	57(2)	51(2)
BMI (kg/m²)	29(1)	31(1)
Ex-smokers (%)	37	26
Smokers (%)	3	5
LABA (%)	98	94
LAMA (%)	32	55
LTRA (%)	73	63
THEO (%)	11	36
INS (%)	100	26
INAH (%)	10	4
PBE (cells/μl)	549(41)	380(31) **
FeNO (ppb)	42(8)	15(3) **
Specific IgE (kUA/L)	0.25(0.08)	0.84(0.34) *
No. of positive specific IgE	1(0.2)	1.6(0.2) *
Total IgE (kU/L)	250(28)	440(69) *
FEV₁%	84(3)	79(2)
FEF₂₅₋₇₅%	42(4)	46(3)
FVC%	106(3)	99(2)
FEV₁/FVC (%)	64(2)	68(2)
R5 (kPa/L/s)	0.45(0.03)	0.60(0.04) **
R5-R20 (kPa/L/s)	0.10(0.02)	0.18(0.03) *
X5 (kPa/L)	-0.14(0.02)	-0.23(0.03) *
AX (kPa/L)	0.89(0.16)	1.79(0.31) *
F_{res} (Hz)	15.59(1.07)	18.68(1.14)
Asthma exac	2(0.3)	4(0.4) ***
ACQ	2.5(0.3)	3.1(0.2)
ICS dose (μg)	1,546(64)	1,892(44) ***

ACQ = asthma control questionnaire; AR = allergic rhinitis; AX = area under reactance curve; AwNP = asthma with nasal polyps; A = asthma without nasal polyps; BMI = body mass index; exac = OCS requiring exacerbations; FeNO = fractional exhaled nitric oxide; FEV₁ = forced expiratory volume in 1 second; FEF₂₅₋₇₅ = forced mid expiratory flow rate between 25 and 75% of forced vital capacity (FVC); F_{res} = resonance frequency; ICS = inhaled corticosteroids; INAH = intranasal antihistamine; INS = intranasal corticosteroid; LABA = long acting beta agonist; LAMA = long acting muscarinic antagonist; LTRA = leukotriene receptor antagonist; PBE = peripheral blood eosinophils; R5 = resistance at 5Hz; R5-R20 = difference in resistance between 5 and 20Hz; THEO = theophylline; X5 = reactance at 5Hz; AwNP vs A p<0.05*; p<0.01**; p<0.001***; FeNO and specific IgE are shown as geometric mean and SEM.

359

360

Table 2

Comparisons between groups according to use of high dose ICS and absence of AR in group A

	ICS $\geq 1,500\mu\text{g}$		AwNP (SEM)	A w/o AR (SEM)
	AwNP (SEM)	A (SEM)		
PBE (cells/ μl)	541(53)	391(34) *	549(41)	387(34) **
FeNO (ppb)	41(9)	15(3) **	42(8)	16(4) **
Specific IgE (kUA/L)	0.25(0.1)	0.77 (0.34)	0.25(0.08)	1.05(0.48) **
No. of positive specific IgE	1.1(0.2)	1.6(0.2)	1(0.2)	1.7(0.2) *
Total IgE (kU/L)	283(40)	467(76)	250(28)	462(81) *
FEV ₁ %	82(3)	80(2)	84(3)	81(2)
FEF ₂₅₋₇₅ %	40(4)	46(3)	42(4)	46(4)
FVC%	104(3)	99(2)	106(3)	101(2)
FEV ₁ /FVC (%)	64(2)	68(2)	64(2)	68(2)
R5 (kPa/L/s)	0.46(0.04)	0.62(0.04) *	0.45(0.03)	0.59(0.05) *
R5-R20 (kPa/L/s)	0.11(0.02)	0.18(0.03)	0.10(0.02)	0.18(0.03) *
X5 (kPa/L)	-0.14(0.03)	-0.24(0.03) *	-0.14(0.02)	-0.22(0.03) *
AX (kPa/L)	0.99(0.19)	1.81(0.30) *	0.89(0.15)	1.81(0.38) *
F _{res} (Hz)	15.81(1.29)	19.26(1.16)	15.59(1.07)	18.53(1.38)
Asthma exac	2.8(0.4)	4(0.3) *	2(0.3)	4(0.4) ***
ACQ	2.7(0.3)	3.2(0.2)	2.5(0.3)	3.1(0.2) *
ICS dose (μg)	1,943(24)	1,997(30)	1,546(64)	1,948(48) ***

Figure 1 Legend

Values shown for asthma patients with or without NP (AwNP vs A), as arithmetic means or geometric (FeNO) and standard error of means, for significant comparisons in overall patient population according to (a) FeNO and PBE count (b) total IgE and number of positive specific IgE and (c) R5-R20 and AX

